

# Use of Tamoxifen in Advanced-Stage Hepatocellular Carcinoma

## A Systematic Review

Anna K. Nowak, M.B.B.S., Ph.D.<sup>1</sup>  
 Martin R. Stockler, M.B.B.S., M.Sc.<sup>1,2</sup>  
 Pierce K. H. Chow, M.B.B.S.<sup>3</sup>  
 Michael Findlay, M.D.<sup>4</sup>

<sup>1</sup> National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, Camperdown, New South Wales, Australia.

<sup>2</sup> Sydney Cancer Centre, Royal Prince Alfred and Concord Repatriation General Hospitals, Camperdown, New South Wales, Australia.

<sup>3</sup> Department of General Surgery, Singapore General Hospital, Singapore, Republic of Singapore.

<sup>4</sup> Cancer Trials New Zealand, University of Auckland, Auckland, New Zealand.

Dr. Anna Nowak is the recipient of the 2003 Medical Oncology Group of Australasia/Novartis Fellowship.

The current study is based on a Cochrane review prepared for the Cochrane Hepato-biliary Group.<sup>37</sup>

Address for reprints: Martin R. Stockler, M.B.B.S., NHMRC Clinical Trials Centre, University of Sydney, Locked Bag 77, Camperdown, New South Wales 1450, Australia; Fax: (011) 612-9562-5000; E-mail: stockler@med.usyd.edu.au

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**BACKGROUND.** Hepatocellular carcinoma (HCC) is the third most common cause of cancer mortality worldwide. Survival is poor for patients with advanced-stage HCC, and small trials of tamoxifen for patients with this disease have shown conflicting results. The authors conducted a systematic review of randomized clinical trials to compare the effect of a tamoxifen-containing arm with a nontamoxifen-containing arm in advanced HCC.

**METHODS.** Eligible trials were identified from the Cochrane Hepato-Biliary Group register and other databases. Studies were selected for inclusion and their methodologic quality assessed by three independent reviewers. Hazard ratios (HR) were derived for overall survival where possible. Metaanalysis was performed using a fixed-effect model.

**RESULTS.** The authors identified 10 randomized trials with a total of 1709 patients. Use of tamoxifen had no effect on median survival (HR, 1.05; 95% confidence interval, 0.94–1.16;  $P = 0.4$ ) or tumor response rate. The findings were stable in sensitivity analyses and were not affected by publication bias or inclusion of low-quality studies or studies reported in abstract form only. Few adverse events or withdrawals were noted.

**CONCLUSIONS.** There was no support for the therapeutic use of tamoxifen in advanced HCC, nor for its use as a control arm in future clinical trials. *Cancer* 2005; **103:1408–14**. © 2005 American Cancer Society.

**KEYWORDS:** anti-estrogen, hepatocellular carcinoma, liver, neoplasm, systemic therapy, tamoxifen.

Worldwide, hepatocellular carcinoma (HCC) is one of the most common causes of death from malignant disease. Although less common in Western populations, it is a significant cause of death in eastern Asia and sub-Saharan Africa.<sup>1</sup> The etiology is believed to be associated primarily with cirrhosis, due to chronic infection with hepatitis B or hepatitis C viruses, alcohol consumption, aflatoxin, or hemochromatosis. People with HCC generally present with advanced-stage disease, although, more recently, some high-risk populations have been targeted for screening, but the outlook is still poor in most stages of the disease.

A variety of therapeutic modalities have been used in these patients.<sup>2</sup> Surgery for early-stage disease results in some long-term survivors. However, the wide applicability of resection is often limited by the poor synthetic function of the cirrhotic liver. The major problem after resection or local ablation is tumor recurrence, which often occurs in the first 24 months after surgery.<sup>3,4</sup> Long-term results similar to those for surgery have been reported with nonsurgical local abla-

**TABLE 1**  
**Search Strategy**

| Register  | Search strategy  | Search date                  |
|---|--|------------------------------|
| Cochrane Hepato-Biliary Group Controlled Trials Register                                  | (carcinoma OR neoplasm* OR cancer) AND (hepat* OR liver) AND (tamoxifen OR antiestrogen* OR anti-estrogen)       | January 2004                 |
| Cochrane Central Register of Controlled Trials on the Cochrane Library                    | (carcinoma OR neoplasm\$ OR cancer) AND (hepat\$ OR liver) AND (tamoxifen OR antiestrogen* OR anti-estrogen)     | Issue 3, 2003                |
| Medline   | (exp CARCINOMA/OR exp Neoplasms/) AND (exp Liver/OR hepat\$.mp) AND (exp Tamoxifen/OR exp Estrogen Antagonists/) | 1966 to November Week 2 2003 |
| Abstracts from the Annual Scientific Meeting of the American Society of Clinical Oncology | Hand searched  | 1996-2003                    |

tive therapies such as percutaneous ethanol injection,<sup>5</sup> radiofrequency ablation,<sup>6</sup> and transarterial chemoembolization.<sup>7</sup> In addition, numerous cytotoxic agents have been investigated in trials comprising patients with HCC,<sup>8</sup> and tumor response rates with systemically administered cytotoxic drugs are generally low, although they may be slightly higher when drugs are administered regionally, with or without embolization.<sup>9</sup> Any benefit from cytotoxic therapy must be weighed against the associated toxicity.

On the basis of the finding that some HCCs have estrogen receptors (ER),<sup>10,11</sup> several trials of the anti-estrogen, tamoxifen, have been conducted. The earliest trials were small and had conflicting results. Although tamoxifen has been used in both women and men with malignant disease, its putative mode of action raises the question of whether its efficacy differs between women and men.

There have been 3 systematic reviews of randomized controlled trials of treatments for HCC.<sup>12-14</sup> Whereas the 2 earlier reviews<sup>12,13</sup> showed a marginal increase in survival with the use of tamoxifen in advanced HCC, both noted that further large, well designed trials were needed to answer this question. The most recent review included further large trials and did not show any survival benefit or antitumor effect for tamoxifen,<sup>14</sup> and the authors noted that only the trials assessed as lower quality showed any benefits.

The current review extended the search beyond Medline and added larger, more recent trials. The primary objective was to assess the effect of tamoxifen on overall survival in patients with HCC. The secondary objectives were to assess the effects of tamoxifen on quality of life, tumor response, and treatment toxicity and, in addition, to assess whether there is an interaction between gender and the effects of tamoxifen on the overall survival or response rate.

**TABLE 2**  
**Eligibility Criteria for Inclusion in the Review**

| Study type              | Unconfounded, truly randomized trials   |
|-------------------------|---|
| Study interventions     | Treatment with any dose or duration of tamoxifen with or without other treatment modalities versus a control arm using placebo, no intervention, best supportive care, or the same other treatment modalities without tamoxifen.  |
| Publication status      | Full publication or abstract.   |
| Participants            | Diagnosis of HCC according to the definitions of individual trials (histology, cytology, or clinical criteria [e.g., typical imaging, raised AFP level, > 5 × upper limit of normal, and a history of chronic liver disease]).  |
| Previous treatment      | Trials recruiting patients with apparently resected disease (testing tamoxifen as an adjuvant treatment) and trials recruiting patients with advanced or unresectable disease (testing tamoxifen as treatment for advanced disease) were both eligible for inclusion; analyses were to be stratified according to the stage of disease. |
| Language of publication | Not restricted.   |

HCC: hepatocellular carcinoma; AFP:  $\alpha$ -fetoprotein.

**MATERIALS AND METHODS**

A search by the secretariat of the Cochrane Hepato-Biliary Group used the search strategy described in Table 1. References of review articles and identified trials were also searched, and experts in the field contacted, but no further trials were identified.

Titles of trials identified through this search strategy were screened for possible eligibility, and the prospectively defined eligibility criteria (Table 2) were applied to each trial by 3 independent reviewers, with disagreements resolved by discussion. Our search identified 42 reports, of which 19 were considered potentially eligible. After further screening of the methods sections of the studies, 10 studies were included. Reasons for excluding trials included the following: no comparison group without tamoxifen,<sup>15-17</sup> confounded controls that added another drug to treat-

TABLE 3  
Study Characteristics

| Study                        | No. of evaluable patients | Control arm                                       | Experimental arm   | Quality grade  | Reference |
|------------------------------|---------------------------|---|--|----------------|-----------|
| Barbare et al., 2002         | 420                       | Placebo use unclear                               | Oral tamoxifen 20 mg daily mg  | — <sup>a</sup> | 35        |
| Castells et al., 1995        | 120                       | Placebo   | Oral tamoxifen 20 mg daily   | A              | 28        |
| Chow et al., 2002            | 324                       | Placebo   | Oral tamoxifen 60 or 120 mg daily  | A              | 26        |
| CLIP-1, 2002                 | 477                       | Supportive care                                   | Oral tamoxifen 40 mg daily   | A              | 29        |
| Coll et al., 1995            | 61                        | Placebo   | Oral tamoxifen 10 mg twice daily   | B1             | 30        |
| Elba et al., 1994            | 22                        | Placebo   | Oral tamoxifen 60 mg daily   | B2             | 34        |
| Liu et al., 2000             | 119                       | Placebo   | Oral tamoxifen 30 mg daily   | B2             | 33        |
| Martinez Cerezo et al., 1994 | 36                        | No treatment                                      | Oral tamoxifen 10 mg twice daily   | B2             | 32        |
| Melia et al., 1987           | 53                        | IV doxorubicin 60 mg/m <sup>2</sup> every 3 weeks | IV doxorubicin 60 mg/m <sup>2</sup> every 3 weeks with tamoxifen 10 mg twice daily | B1             | 27        |
| Riestra et al., 1998         | 77                        | Placebo   | Oral tamoxifen 40 mg daily   | B1             | 31        |

i.v.: intravenous.

<sup>a</sup> Inadequate information available in abstract to classify quality.

ment in place of tamoxifen,<sup>18</sup> studies that were not actually assessing the effect of tamoxifen,<sup>19</sup> studies that were assessing the affect of combination hormonal therapy with tamoxifen and medroxyprogesterone acetate,<sup>20</sup> studies in which the outcome measures were unsuitable for analysis,<sup>21</sup> studies with nonrandomized allocation to treatment and control arms,<sup>22,23</sup> and publications that were found to be review articles.

Methodologic quality was assessed independently by 3 reviewers using a modified subset of the MERGE criteria,<sup>24</sup> based on standard criteria to assess the degree to which the study is susceptible to bias. The criteria specifically take into account concealment of treatment allocation, generation of the allocation sequence, blinding of treatment delivery, comparability between groups at baseline, inclusion of all randomized participants in the analysis, withdrawals from the trial, and valid assessment of end points. A global rating of quality and susceptibility to bias was then assigned as follows: A) all or most criteria fulfilled: where not fulfilled, it is believed very unlikely that the conclusions of the study would be altered; B1) some criteria are fulfilled: where not fulfilled, it is believed unlikely that the conclusions of the study would be altered; B2) some criteria are fulfilled: where not fulfilled, it is believed likely that the conclusions of the study would be altered; C) few or no criteria are fulfilled: where not fulfilled, it is believed very likely that the conclusions of the study would be altered.

Survival data were obtained indirectly using the methods described by Parmar et al.,<sup>25</sup> by recording actuarial survival proportions at predetermined time points from Kaplan–Meier curves or tables. Censoring was accounted for by adjusting the numbers at risk on

the basis of actual (where available) or estimated maximum and minimum follow-up times. To calculate an overall estimate of effect but avoid including the control group twice, the 3-arm study<sup>26</sup> was analyzed using one-half of the control group numbers as controls for each of the 2 experimental arms. A fixed-effect model was used to calculate a pooled hazard ratio (HR) for overall survival, using the derived observed minus expected number of events and the variance obtained for each trial.<sup>25</sup> The 95% confidence intervals (95% CI) were calculated for individual and aggregate estimates of effect.

## RESULTS

Of the 10 trials selected, 8 were fully reported, 2 were published in abstract form only, and 1709 patients were included (Table 3). Nine studies examined the effect of tamoxifen versus placebo or no treatment on outcomes that included overall survival. One study randomized patients to 2 different doses of tamoxifen in 2 arms in addition to the control arm.<sup>26</sup> A single study examined the effect of adding tamoxifen to chemotherapy with doxorubicin.<sup>27</sup>

### Quality of the Studies

The methodologic quality of the studies was variable, with a low risk of bias in 3 trials (Grade A: 27%),<sup>26,28,29</sup> a low to moderate risk in 3 trials (Grade B1: 27%),<sup>27,30,31</sup> and moderate to high risk in 3 trials (Grade B2: 18%).<sup>32–34</sup> Inadequate information was available to classify 1 further study, published in abstract form only.<sup>35</sup> Six studies were placebo controlled,<sup>26,28,30,31,33,34</sup> although the study by Liu et al. was single-blinded only,<sup>33</sup> and the adequacy of blind-

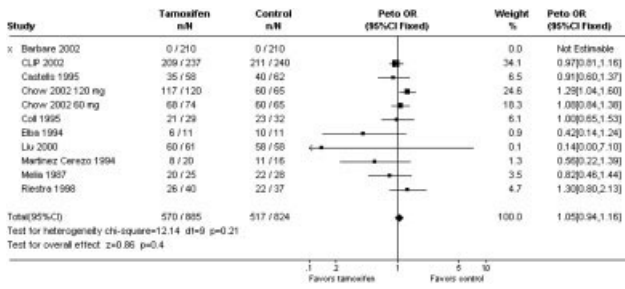


FIGURE 1. Effect of tamoxifen on overall survival.

ing in a further 2 studies was unclear.<sup>30,34</sup> The remainder were either not placebo controlled<sup>27,29,32</sup> or this information was not available.<sup>35</sup>

**Patient Characteristics**

The characteristics of patients in these 10 trials appeared similar. Their mean age ranged from 60 to 67 years in the 9 studies testing tamoxifen alone, but was lower (52 years) in the study testing tamoxifen with doxorubicin.<sup>27</sup> Most patients were male in all studies (range, 71–89%). Underlying liver disease was reported in 98–100% of patients. Most studies excluded patients with advanced concomitant liver disease, with all studies including < 25% of patients with Child–Pugh Stage C liver disease, and < 25% of patients with Okuda Stage III disease. Only 1 study reported including patients who had previously undergone either surgery (5% of patients) or chemotherapy (16% of patients).<sup>29</sup>

**Effect of Tamoxifen Treatment on Overall Survival**

In metaanalysis, overall survival was not affected by the addition of tamoxifen (odds ratio, 1.05; 95% CI, 0.94–1.16; *P* = 0.4) (Fig. 1). This comparison showed no significant statistical heterogeneity (*P* = 0.2). One trial of 420 patients was necessarily excluded from the metaanalysis because it reported insufficient data.<sup>35</sup> However, it is unlikely that the availability of these data would change the overall review conclusions, as the trial showed no significant difference in median survival between the tamoxifen and control arms.

Exclusion of the single trial published in abstract form only for which results were available<sup>30</sup> did not affect the results of the analysis (HR, 1.05; 95% CI, 0.94–1.17; *P* = 0.4). Median survival for both experimental and control arms was available for all studies reviewed, but was very variable, suggesting that the patient groups were more heterogeneous than the patient characteristics suggested. Median survival in the control arm ranged from just over 1 month<sup>33</sup> to 12 months<sup>34</sup> in groups without any previous surgical

treatment, and as high as 16 months in the study allowing previous surgery.<sup>29</sup>

Funnel plots suggest the possibility of publication bias, as there were several small trials with positive results, but no corresponding small trials with negative results. The inclusion of unpublished and unidentified small trials with negative results could potentially show an overall detrimental effect of tamoxifen. None of the three trials showing a low potential for bias showed any survival benefits for tamoxifen. However, this may be confounded by the use of higher doses of tamoxifen in the studies showing the lowest potential for bias.

The stratification of analyses according to stage of disease (i.e., postresection vs. advanced disease) was planned, but could not be performed as no studies included only postresection patients. Analysis using only studies with histologic or cytologic confirmation of the diagnosis was also planned originally. However, only 1 study, of 61 patients and overall poor quality, fulfilled these criteria,<sup>30</sup> and hence this analysis was not done. In a further 5 trials, either histologic diagnosis or an elevated  $\alpha$ -fetoprotein level together with imaging suggestive of HCC was accepted.<sup>27,29,31–33</sup> In these studies, a diagnosis was made without histology or cytology examinations in 17%, 14%, 17%, 25%, and 24% of patients, respectively. A further 2 studies accepted similar criteria for diagnosis, but did not report the number of diagnoses made without histology or cytology.<sup>26,28</sup> Criteria for the diagnosis of HCC were not reported in 2 studies.<sup>34,35</sup>

**Effect of Tamoxifen Dosage**

It has been hypothesized previously that higher doses of tamoxifen could be more effective by invoking estrogen receptor-independent mechanisms of tumor inhibition.<sup>36</sup> In the trials identified, the daily dose of tamoxifen varied, ranging from 20 mg in 5 trials,<sup>27,28,30,32,35</sup> 30 mg in 1 trial,<sup>33</sup> 40 mg in 2 trials,<sup>29,31</sup> to 60 mg in 1 trial.<sup>34</sup> A single 3-arm study randomized patients to 2 high-dose levels of tamoxifen, 60 or 120 mg daily, or placebo.<sup>26</sup> In subgroup analysis, there was an overall survival trend favoring the control arms with higher doses of tamoxifen (Fig. 2). The HR for overall survival was lowest for trials of tamoxifen 20 mg daily (HR, 0.88; 95% CI, 0.69–1.44; *P* = 0.71), higher in trials of tamoxifen 40 mg daily (HR, 1.00; 95% CI, 0.85–1.19; *P* = 1.0), higher still in trials of tamoxifen 60 mg daily (HR, 1.03; 95% CI, 0.81–1.31; *P* = 0.8), and highest in the single trial of tamoxifen 120 mg daily (HR, 1.29; 95% CI, 1.04–1.6; *P* = 0.02). There is unlikely to be a place for further trials of tamoxifen dose escalation in this setting.

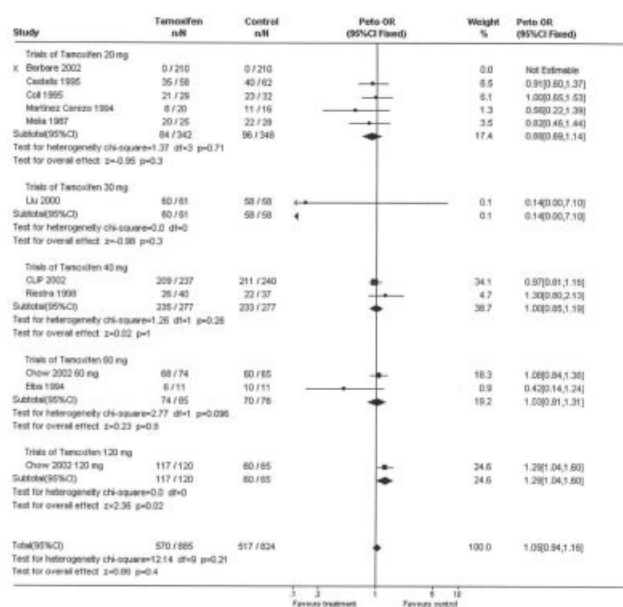


FIGURE 2. Effect of tamoxifen dosage on overall survival.

**Effect of Gender on Overall Survival**

The influence of gender on treatment effects was not an a priori objective in any of the trials. One trial reported no difference in survival between men and women in post-hoc analysis.<sup>28</sup> One trial reported a significant benefit of tamoxifen for men without major hepatic insufficiency ( $P = 0.02$ ) but no benefit for women ( $P = 0.59$ ).<sup>35</sup> There were insufficient data for a metaanalysis on these subgroups. There was no comment on gender differences in the only study to report estrogen receptor status in tumors.<sup>33</sup> Furthermore, ER status did not correlate with outcome in this trial.

**Objective Tumor Responses and  $\alpha$ -Fetoprotein Responses**

Assessment of tumor or serologic response was not an a priori objective of any trial. Radiologic response was reported in only 4 trials,<sup>27,28,30,33</sup> and in these, tumor response rates were not affected by the addition of tamoxifen. Although the response criteria were not defined, Coll et al.<sup>30</sup> reported no partial responses (PR) and similar rates of progressive disease between treated and untreated groups (78% vs. 79%). Castells et al.<sup>28</sup> reported 1 PR (World Health Organization criteria) in the placebo group and the development of progressive disease was not different between the 2 groups. Liu et al.<sup>33</sup> reported no PRs and similar rates of progressive disease at 3 months (54% without tamoxifen vs. 43% with tamoxifen). In the single trial combining tamoxifen with chemotherapy, Melia et al.<sup>27</sup> reported a PR rate of 11% in the group receiving doxo-

rubicin alone, and 16% in the group receiving doxorubicin plus tamoxifen, a difference that was not statistically significant. There is no evidence that tamoxifen can produce objective tumor responses.

**Quality of Life**

Quality of life was examined in only 1 study using a validated tool (the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire), but the data were not presented in detail.<sup>26</sup> The authors commented that there were no appreciable differences in global quality of life between the treatment groups and that scores seemed somewhat lower with the highest dose of tamoxifen (120 mg). Thus, there is no evidence that tamoxifen can produce quality-of-life benefits in these patients.

**Toxicity**

Treatment toxicity was not described as a predefined outcome in any study and was reported inconsistently. Reports of 2 trials made no mention of toxicity,<sup>27,30</sup> whereas reports of 3 trials only included comments that treatment was “well tolerated” or had “negligible” or “minimal” toxicity.<sup>28,31,33</sup> Reports of 3 trials described minor side effects such as diarrhea, thrombophlebitis, vertigo, and hot flashes in a few patients.<sup>32,34,35</sup> The 2 largest trials reported toxicity in more detail.<sup>26,29</sup> Chow et al.<sup>26</sup> graded toxicity as mild, moderate, or severe, with 3% of patients developing moderate or severe toxicity, with equal numbers receiving tamoxifen and placebo, and in this trial 1.5% of patients receiving tamoxifen withdrew from treatment because of toxicity. The CLIP-1 investigators<sup>29</sup> reported that 10% of patients receiving tamoxifen developed toxicity, and 4% stopped tamoxifen because of toxicity. A surprising absence was that none of the trial reports described thromboembolic events. This may reflect either coagulopathy from underlying liver disease or lack of rigor in reporting adverse events.

**DISCUSSION**

We identified 10 randomized trials testing tamoxifen in 1709 people with HCC and found no evidence of benefit. There were no apparent effects on survival, tumor response rate, or quality of life. Furthermore, the trials with the least risk of bias tended to show that tamoxifen was associated with increased mortality, whereas the trials with the largest risk of bias showed the opposite effect.

Funnel plots suggested publication bias, with several small positive trials and no corresponding small negative trials. It is possible that there are additional, small, unpublished negative trials. Their inclusion would improve the rigor of the current review, but

would not affect its conclusion, namely, that the available evidence argues against use of tamoxifen in HCC.

Many trials identified were of low methodologic quality, with only two trials assessed as showing a low potential for bias. Our findings that tamoxifen seemed to increase mortality in high-quality trials but have the opposite effect in low-quality trials support the contention that low-quality trials are susceptible to bias. However, we were not able to determine whether the difference in treatment response was due to the methodologic quality of the trials or the dose of tamoxifen, as this finding is confounded by the use of higher doses of tamoxifen in the better-quality trials.

These data argue against the use of tamoxifen in advanced HCC. Further research on the effects of tamoxifen in HCC is probably unwarranted. Tamoxifen should not be used as a control arm in trials in HCC. Future promising interventions should be tested in large, well designed, randomized controlled clinical trials.

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